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Infection With GB Virus C and Hepatitis C Virus in Hemodialysis Patients and Blood Donors in Beijing

Yu Wang,[1] Hong-Song Chen,[1] Min-Hua Fan,[2] Hui-Lan Liu,[3] Ping An,[4] Naoto Sawada,[5] Takeshi Tanaka,[6] Fumio Tsuda,[7] and Hiroaki Okamoto[8]*

[1]*Institute of Hepatology, People's Hospital, Beijing Medical University, Beijing, China*
[2]*Department of Nephrology, the Third Hospital, Beijing Medical University, Beijing, China*
[3]*Department of Nephrology, Fu Xing Hospital, Capital Medical University, Beijing, China*
[4]*Chinese PLA Institute of Liver Disease, Beijing, China*
[5]*Institute of Immunology, Tokyo, Japan*
[6]*Japanese Red Cross Saitama Blood Center, Saitama-Ken, Japan*
[7]*Department of Medical Sciences, Toshiba General Hospital, Tokyo, Japan*
[8]*Immunology Division, Jichi Medical School, Tochigi-Ken, Japan*

RNAs of GB virus C (GBV-C) and hepatitis C virus (HCV) were sought by reverse-transcription polymerase chain reaction with nested primers deduced from the 5′ untranslated region: 79 patients on maintenance hemodialysis, 205 commercial blood donors, and 205 voluntary donors in Beijing were studied. GBV-C RNA was detected in 43 (54%) patients and 17 (8%) commercial donors, and HCV RNA in 43 (54%) patients and 13 (6%) commercial donors, respectively. By contrast, GBV-C RNA was detected only in 2 (1%) and HCV RNA in none among 205 volunteer blood donors serving as controls. Thus both patients and commercial blood donors were at higher risk for infection with GBV-C ($P < 0.001$) than controls. HCV RNA was detected more often in patients with GBV-C RNA than without (29/43 or 67%, vs. 14/36 or 39%, $P < 0.05$) as well as in commercial donors with GBV-C RNA than without (5/17 or 29% vs. 8/188 or 4%, $P < 0.01$). A phylogenetic tree constructed on a sequence of 100 base pairs in the helicase region indicated that GBV-C isolates from Beijing are more similar to Japanese isolates than to isolates from the United States and Africa. Sequences from certain hemodialysis patients and those from some commercial donors were similar, suggesting nosocomial infection and spread among restricted groups. ***J. Med. Virol. 52:26–30, 1997.***

KEY WORDS: hepatitis viruses; hepatitis C virus; viral hepatitis; hemodialysis; transfusion; epidemiology

INTRODUCTION

There appear to be hepatitis viruses other than hepatitis A, B, C, D, or E which may be responsible for cryptogenic hepatitis and cirrhosis [Alter and Bradley, 1995]. A putative agent for non-A to E hepatitis has been discovered independently by two research groups and named GB virus C (GBV-C) and hepatitis G virus (HGV), respectively [Simons et al., 1995; Leary et al., 1996; Linnen et al., 1996]. They are both positive stranded RNA viruses of 9400 nucleotides and have genomic organizations resembling those of flaviviridae and hepatitis C virus (HCV), in particular; their sequence is too divergent for them to be classified as genotypes of HCV. GBV-C and HGV, however, share 86% of nucleotide and more than 96% of amino acid sequences, and are therefore considered to be possibly different genotypes of the same virus.

The hepatitis-inducing activity of GBV-C/HGV is yet to be determined. Posttransfusion or community acquired non-A to E hepatitis runs a mild subclinical course [Alter and Bradley, 1995], and most cases of fulminant hepatitis today are not associated with markers of known hepatitis viruses [Feray et al., 1993; Wright, 1993]. GBV-C RNA has been reported in some patients with fulminant non-A to E hepatitis [Yoshiba et al., 1995], and it may be responsible for a part of cryptogenic hepatitis and cirrhosis [Fiordalisi et al., 1996]. Furthermore, GBV-C/HGV may either cooperate or interfere with the other hepatitis viruses, resulting in the aggravation or amelioration of hepatitis [Purcell,

*Correspondence to: Dr. H. Okamoto, Immunology Division, Jichi Medical School, Minamikawachi-Machi, Tochigi-Ken 329-04, Japan.

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TABLE I. Markers of Hepatitis Virus Infections in Hemodialysis Patients, Commercial, and Voluntary Blood Donors in Beijing, China

	N	Male	Age (years)	GBV-C RNA	HCV RNA	Anti-HCV	HBsAg	Anti-HBc[a]
Hemodialysis patients	79	48 (61%)	51 ± 13	43 (54%)	43 (54%)	32 (41%)	7 (9%)	65 (82%)
Commercial blood donors	205	87 (42%)	31 ± 6	17 (8%)	13 (6%)	21 (10%)	5 (2%)	43 (21%)
Voluntary blood donors	205	115 (56%)	38 ± 11	2 (1%)	0	3 (2%)	7 (3%)	60 (29%)

[a]Patients or donors who were positive for anti-HBc in the absence of HBsAg.

1994]. Co-infection of GBV-C/HGV with HCV has been reported to be frequent [Simons et al., 1995; Egawa et al., 1996; Linnen et al., 1996; Masuko et al., 1996]. This may reflect common routes of infection with these two viruses in medical institutions and restricted groups typified by hemodialysis patients and users of illicit intravenous drugs.

Patients on hemodialysis and commercial blood donors in Beijing, China, were tested for GBV-C RNA and HCV RNA. A partial nucleotide sequence in the nonstructural 3 (NS3) or helicase region of GBV-C was then compared among them and with reported sequences to investigate the origin of this virus and the way it might have spread.

SUBJECTS AND METHODS

Patients and Blood Donors

During January and February of 1994, 79 patients (48 male, 31 female; age 51 ± 13 years) received hemodialysis in 4 dialysis centers in Beijing. They included 13 patients in People's Hospital, Beijing Medical University, 37 in Fu Xing Hospital, 19 in Beijing Medical University Hospital, and 10 in Beijing Military Hospital. In October 1995, blood units were purchased from 205 commercial donors (87 male, 118 female; age 31 ± 6 years). They were mostly farmers in the suburbs of Beijing and sold blood repeatedly so long as they were negative for hepatitis B surface antigen (HBsAg) and had levels of alanine aminotransferase (ALT) within normal range (<40 IU/L). Serving as controls were 205 workers in a factory of Beijing (115 male, 90 female; age 38 ± 11 years) who donated blood voluntarily. They all received hepatitis B vaccines, provided that they were negative for HBsAg in serum.

Sera were tested for serological markers of HCV and hepatitis B virus (HBV) infections. Portions of sera that had been stored at −80°C were tested for GBV-C RNA and HCV RNA.

Detection of GBV-C RNA and Sequencing

GBV-C RNA was determined in RNAs extracted from 100 μl of test serum by reverse-transcription (RT) polymerase chain reaction (PCR) with nested primers deduced from conserved areas in the 5′ untranslated region (UTR) of reported GBV-C/HGV genomes by the method reported previously [Shimizu et al., 1996]. A sequence of 100 base pairs in the NS3 region was determined in GBV-C isolates amplified by RT-PCR by the method described elsewhere [Yoshiba et al., 1995; Masuko et al., 1996].

HCV RNA and Genotypes

RNAs were extracted from 100 μl of test serum, and HCV RNA was determined by RT-PCR with nested primers deduced from the 5′UTR [Okamoto et al., 1994]. Genotypes of HCV were determined by selective amplification by a second-generation PCR method with type-specific sense as well as antisense primers which had been deduced from the core gene [Okamoto et al., 1996]. The results were recorded by the mixed naming system of Okamoto et al. [1993] and Simmonds et al. [1993], such as I/1a, II/1b, III/2a, IV/2b, and V/3a.

Serological Tests

HBsAg and antibody to HBsAg (anti-HBs) were determined by passive hemagglutination with commercial kits (MyCell, Institute of Immunology Co., Ltd., Tokyo, Japan) and antibody to hepatitis B core (anti-HBc) by hemagglutination inhibition [Iizuka et al., 1992]. Subtypes of HBsAg were determined by enzyme-linked immunosorbent assay with commercial kits (Institute of Immunology Co., Ltd.). Antibody to HCV (anti-HCV) was determined by enzyme-linked immunosorbent assay of the third generation (Ortho ELISA III, Ortho Diagnostic Systems, Tokyo, Japan) with an absorbance at 492 nm exceeding 0.65 considered positive.

Phylogenetic Tree

A phylogenetic tree of GBV-C was constructed by the unweighted pair-group method with arithmetic mean of Nei [1987] using a molecular evolutionary analysis system for DNA and amino acid sequences (treeupg of the ODEN programs version 1.1.1, National Institute of Genetics, Mishima, Japan).

Statistical Analysis

Frequencies between groups were compared using the Fisher's exact test and χ^2 test, and group means were compared using the Student's *t*-test.

RESULTS

Hepatitis Virus Infections in Hemodialysis Patients and Blood Donors in Beijing

GBV-C RNA was detected in 43 (54%) of 79 hemodialysis and 17 (8%) of 205 commercial blood donors in Beijing, more frequently than in 2 (1%) of 205 voluntary blood donors serving as controls ($P < 0.001$ and $P < 0.01$, respectively) (Table I). There were no sex differences in the prevalence of GBV-C RNA either in he-

modialysis patients (26/48 or 54% of males and 17/31 or 55% of females) or in commercial blood donors (7/87 or 8% of males and 10/118 or 8% of females).

HCV RNA was detected in 54% of hemodialysis patients and anti-HCV in 41%, more frequently than in 0% and 2% of voluntary blood donors ($P < 0.01$ and $P < 0.001$, respectively). Although individuals with elevated ALT were deferred, HCV RNA was detected in 6% and anti-HCV in 10% of commercial blood donors, more frequently than in voluntary blood donors ($P < 0.001$).

The prevalence of GBV-C RNA in hemodialysis patients varied widely among the 4 dialysis centers; it was detected in 4 of 13 patients or 31%, 4/10 or 40%, 8/19 or 42%, and 27/37 or 73%. Such a distribution paralleled the prevalence of HCV RNA which was detected in 23%, 20%, 47%, and 78% in the respective dialysis centers.

HBsAg was detected in 9% of hemodialysis patients somewhat more frequently than in 3% of voluntary blood donors, while anti-HBc unaccompanied by HBsAg was more common in the former than the latter (82% vs. 29%, $P < 0.001$); anti-HBs did not always represent resolved infection because all the HBsAg-negative voluntary blood donors had received hepatitis B vaccine. There were no significant differences in the prevalence of HBsAg (2% vs. 3%) or anti-HBc unaccompanied by HBsAg 21% vs. 29% between commercial and voluntary blood donors; individuals with HBsAg were deferred from commercial blood donors.

There were 16 patients on maintenance hemodialysis who tested positive for HCV RNA in the absence of anti-HCV, who corresponded to 37% of the 43 patients with HCV RNA. Five such patients with seronegative HCV infection were tested again after 4 months, and they had all become anti-HCV positive.

HCV, HBV, and GBV-C Markers in Hemodialysis Patients and Commercial Blood Donors

Demographic features, elevated alanine aminotransferase (ALT) levels, and markers of HCV and HBV infections were compared between hemodialysis patients and commercial blood donors with and without GBV-C RNA (Table II and Table III). None had elevated levels of ALT, irrespective of the presence or absence of GBV-C RNA. Hemodialysis patients with GBV-C RNA had higher prevalence rates of HCV RNA ($P < 0.05$), anti-HCV ($P < 0.05$), or at least one of them ($P < 0.01$) than those without. Likewise, commercial blood donors with GBV-C RNA had higher prevalence rates of HCV RNA ($P < 0.01$), anti-HCV ($P < 0.001$), or at least one of them ($P < 0.001$) than those without.

Molecular Investigation of GBV-C in Commercial Blood Donors and Hemodialysis Patients in Beijing

Sequences of 100 base pairs in the NS3 (helicase) region were determined for all GBV-C isolates from the 17 commercial blood donors with GBV-C infection (CCD1–17), along with those from 5 each hemodialysis patients with GBV-C RNA randomly selected in 2 dialysis centers in Beijing (CHD1–10). A phylogenetic tree was then constructed on them, along with 21 sequences of reported GBV-C or HGV isolates [Simons et al., 1995; Yoshiba et al., 1995; Linnen et al., 1996; Masuko et al., 1996], as illustrated in Fig. 1. GBV-C isolates from some commercial donors had identical sequences: CCD2–4; CCD7–11; CCD13–15. Similarly, sequences from the 2 hemodialysis patients in the same dialysis unit were identical (CHD8 and CHD9). Sequences from commercial blood donors and hemodialysis patients in Beijing were more close to Japanese iso-

TABLE II. Demographic Features, Elevated Transaminase, and Markers of HCV and HBV Infections in Hemodialysis Patients With and Without GBV-C RNA

	GBV-C RNA		
	Positive	Negative	Differences
N	43	36	
Age (yr)	50 ± 13	53 ± 13	
Male (%)	26 (60%)	22 (61%)	
ALT elevated (≥40 IU/L)	17 (40%)	10 (28%)	
ALT (IU/L)	44 ± 47	37 ± 48	
HCV RNA	29 (67%)	14 (39%)	$P < 0.05$
Genotype II/1b	23 (53%)	13 (36%)	
Genotype III/2a	5 (12%)	0	
Genotype II/1b + III/2a	1 (2%)	1 (3%)	
Anti-HCV	23 (53%)	9 (25%)	$P < 0.05$
HCV infection[a]	33 (77%)	15 (42%)	$P < 0.01$
HBsAg	6 (14%)	1 (3%)	
Subtype *adr*	5 (12%)	1 (3%)	
Subtype *adw*	1 (2%)	0	
Anti-HBc/s[b]	33 (77%)	33 (92%)	
HBV infection[c]	39 (91%)	34 (94%)	

[a]Patients with HCV RNA, anti-HCV, or both.
[b]Patients with anti-HBc, anti-HBs, or both, in the absence of HBsAg.
[c]Patients with at least one of HBsAg, anti-HBc, and anti-HBs.

TABLE III. Demographic Features, Transaminase, and Markers of HCV and HBV Infections in Commercial Blood Donors With and Without GBV-C RNA

	GBV-C RNA		
	Positive	Negative	Differences
N	17	188	
Age (yr)	29 ± 5	31 ± 6	
Male (%)	7 (41%)	80 (43%)	
ALT elevated (≥40 IU/L)	0	0	
HCV RNA	5 (29%)	8 (4%)	$P < 0.01$
Genotype II/1b	5	4	
Genotype III/2a	0	4	
Anti-HCV	8 (47%)	13 (7%)	$P < 0.001$
HCV infection[a]	8 (47%)	13 (7%)	$P < 0.001$
HBsAg[b]	0	5 (3%)	
Subtype *adr*	0	2	
Subtype *adw*	0	1	
Subtype *ayr*	0	2	
Anti-HBc/s[c]	4 (24%)	71 (38%)	
HBV infection[d]	4 (24%)	76 (40%)	

[a]Donors with HCV RNA, anti-HCV, or both.
[b]Of 205 voluntary blood donors, 7 (3%) were positive for HBsAg; subtypes were *adr* in 4, *adw* in 2, and *ayr* in 1.
[c]Donors with anti-HBc, anti-HBs, or both, in the absence of HBsAg.
[d]Donors with at least one of HBsAg, anti-HBc, and anti-HBs.

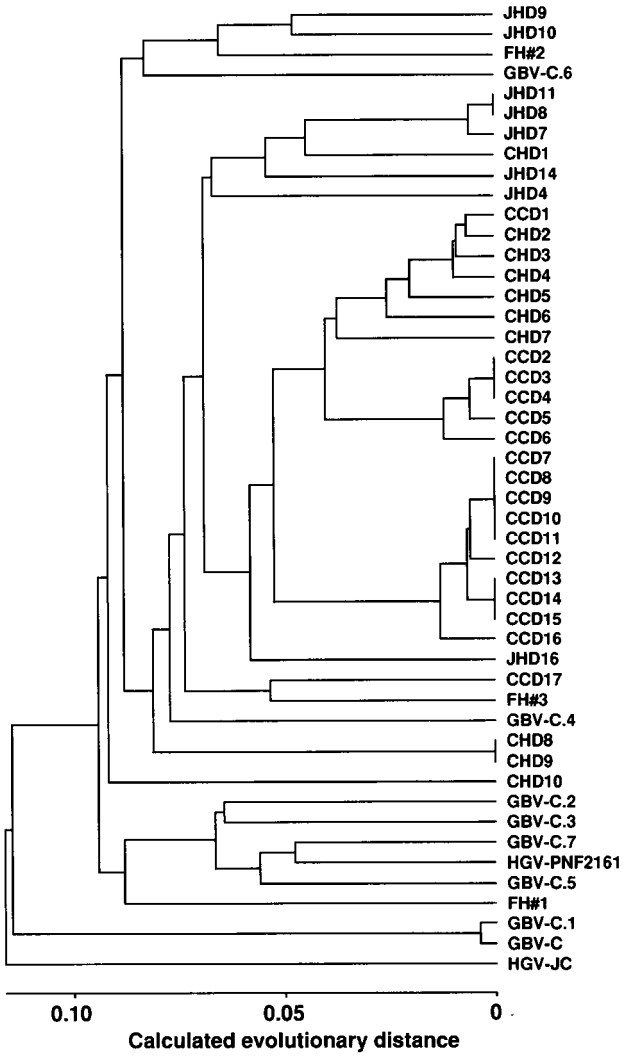

Fig. 1. A phylogenetic tree of GB virus C and hepatitis G virus. A sequence of 100 base pairs in the non-structural 3 (helicase) region was determined in GBV-C isolates from 17 commercial blood donors (CCD1–17) and 10 hemodialysis patients (CHD1–10) in Beijing, China. They were compared with each other, with those from the hemodialysis patients (JHD4, JHD7–11, JHD14 and JHD16) [Masuko et al., 1996], with the patients with fulminant hepatitis (FH#1–3) [Yoshiba et al., 1995] in Japan, and with those from the hepatitis patients and healthy individuals in the United States, Canada, and Africa (GBV-C, GBV-C.1–7, HGV-PNF2161 and HGV-JC) [Simons et al., 1995; Linnen et al., 1996].

lates (FH#1–3, JHD4, JHD7–11, JHD14, JHD16) than to American or African isolates (GBV-C, GBV-C.1–7, HGV-PNF2161, HGV-JC).

DISCUSSION

GBV-C RNA was detected in 43 (54%) of 79 patients on maintenance hemodialysis in Beijing, China, much more frequently than in 2 (1%) of 205 voluntary blood donors serving as controls ($P < 0.001$). It was detected in between in 17 (8%) of 205 commercial blood donors. The prevalence in voluntary blood donors (1%) was comparable with that in 0.9% of 448 Japanese blood donors [Masuko et al., 1996] and 1.7% of 769 blood donors in the United States [Linnen et al., 1996].

Although GBV-C or HGV infection prevails in hemodialysis patients, the frequency varies widely from country to country. GBV-C/HGV RNA in hemodialysis patients is reported to be 3.1% in Japan [Masuko et al., 1996], 20% in the United States and Europe [Alter, 1996], 55% in Indonesia [Tsuda et al., 1996], and 58% in France [de Lamballerie et al., 1996]. The high rate of GBV-C/HGV infection in hemodialysis patients may be ascribable to transfusions they receive. It would be attributable, also, to the nosocomial infection during hemodialysis. The prevalence of GBV-C RNA varied widely in the four dialysis center in Beijing from 31 to 73%, which was in parallel with the detection of HCV RNA, ranging from 20 to 78%.

The two different routes of spread of GBV-C infection among hemodialysis patients may be distinguished by sequencing a part of the viral genome. Transmission by transfusions would result in unique sequences differing among patients, while patient-to-patient spread would lead to identical sequences being shared by some. Two of the patients had the same sequence within 100 base pairs in the NS3 (helicase) region, pointing to a nosocomial transmission, as has been indicated among Japanese hemodialysis patients [Masuko et al., 1996].

Sequence comparison of GBV-C isolates from commercial blood donors in Beijing disclosed clustering of the same sequences among them; three, three, and five blood donors, respectively, were infected with GBV-C having the same sequences of 100 base pairs in the NS3 region. Hence common sources of GBV-C infection prevailed in them, which might have been transmitted by paramedical practices like acupuncture or shared needles for illicit intravenous drugs. Alternatively, they could have been transmitted with GBV-C while they sold blood repeatedly.

Sequences from the commercial blood donors and hemodialysis patients in Beijing were close to each other, and they resembled those from the patients on maintenance hemodialysis [Masuko et al., 1996] or with fulminant hepatitis in Japan [Yoshiba et al., 1995] rather than those from the hepatitis patients and healthy individuals in the United States and Africa [Simons et al., 1995; Linnen et al., 1996]. Therefore, Chinese and Japanese GBV-C strains may have a closely related ancestry which is probably different from American and African strains.

High prevalence rates of GBV-C/HGV RNA have been reported in HCV carriers [Linnen et al., 1996; Masuko et al., 1996; Tsuda et al., 1996], indicating that they tend to co-infect. Both for hemodialysis patients and commercial blood donors in Beijing, HCV RNA was detected more frequently in those with GBV-C RNA than without (67% vs. 39% ($P < 0.05$) and 29% vs. 4% ($P < 0.01$), respectively). Hence, GBV-C and HCV would seem to have common routes of infection. It has to be evaluated whether GBV-C and HGV would cooperate

or interfere with each other in aggravating or ameliorating the symptoms of chronic hepatitis C.

Surprisingly, HCV RNA in 16 (37%) of the 43 hemodialysis patients was not accompanied by anti-HCV. Compromised immune responses found in hemodialysis patients may have prevented seroconversion to anti-HCV [Goldblum and Reed, 1980], or they may have been infected recently and be in the window period. All 4 patients with seronegative HCV infection developed anti-HCV within 4 months, which is in favor of the latter view. Such a constant exposure of hemodialysis patients to HCV would point to a continuing high risk also for GBV-C.

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